

REMARKS

1. Procedural Matters

1.1. A petition to withdraw finality was filed October 15, 2008 but has not yet been decided.

If the petition is granted, this amendment should be entered as a matter of right.

If the petition is denied, this amendment should be entered as it presents the rejected claims in better form for appeal.

1.2. The Examiner does not appear to have addressed §1.1 of our January 29, 2008 response.

2. Claim Amendments; Prior Art Issue; Objections

Claim 1 has been amended to incorporate the limitation of 39, which in turn is now cancelled as redundant.

Claims 38 and 41 have been amended to incorporate the limitation of claim 40, which in turn is now cancelled as redundant.

**The above amendments moot the prior art rejection, which was not applied to claims 39 and 40.**

Claim 38 has been amended to moot that part of the enablement rejection which was directed at the term "prophylactically effective", by deleting that term. We considered administration prior to or during gastromectization to constitute prophylaxis and therefore deleted both. Since claim 41 was and is directed to prophylaxis, we added the "during gastromectization" option to that claim. This was, of course, previously the subject of claim 38 and we are simply transferring that embodiment from claim 38 to claim 41.

Claims 38 and 41 has also been amended to correct the typographical errors noted on page 2.

3. Unity of Invention

Since the prior art rejection is overcome by the amendments to claims 1, 38 and 41, the restrictions should be withdrawn.

First, the restriction mailed Sept. 21, 2005 restricted between a subcombination (group I) and a combination (group II). In response, on Oct. 23, 2006, we elected group I. The combination claims 18 and 20 are dependent on claim 1, which is free of the prior art. Hence, they must be rejoined in accordance with the PCT Administrative Instructions, Annex B, part 1, para. (c)(1) as explained in that response. Indeed, the paper mailed January 23, 2007, page 3, conceded that if one or more Group I claims were found allowable, claims 18 and 20 will likely be rejoined.

Secondly, that restriction also imposed various species restrictions, all of which were traversed. Claims 1, 38 and 41 (at least) being free of the art, the species restriction in question should be withdrawn. In this regard, the examiner is reminded of the PCT "genus/species" unity rules, which were discussed in the second supplemental election with traverse filed Feb. 21, 2007.

#### 4. Enablement (OA pp. 3-5)

After entry of the amendment, the sole issue remaining is the propriety of the enablement rejections.

4.1. The present claims require that the gastrectomy be, as is the norm<sup>1</sup>, accompanied by vagotomy.

The Asakawa reference teaches that Ghrelin is ineffective in a vagotomised individual, which according to the Examiner therefore suggests that the present invention is not enabled.

In rebuttal thereof, we submit:

(1) the present application provides experimental evidence demonstrating increased body weight in gastrectomized and

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<sup>1</sup> See Jansson Declaration filed January 29, 2008, section 10.

vagectomized<sup>2</sup> rats after administration of a ghrelin analogue (MK677)

2) the increase in body weight in the MK677-treated rats is fairly inferred to be the result of the action of MK677 on a ghrelin receptor not eliminated by the vagectomization,

3) ghrelin would be expected to be able to act upon that same ghrelin receptor and thus to have a similar effect in a vagectomized individual,

4) there is also direct evidence that ghrelin can increase body weight in a vagectomized individual,

5) there are a variety of plausible reasons why Asakawa would not have observed appetite stimulation by ghrelin in a vagectomized individual.

Consequently, even if Asakawa were deemed to establish a prima facie case of non-enablement, that case is rebutted.

#### Point 1

As we pointed out previously, in our Example 1, the "gastrectomy was accompanied by total vagotomy at the level of cardia", but animals treated with the ghrelin analogue MK-0677 (page 47, line 29 and page 48, lines 4-5) nonetheless experienced a gain in body weight.

#### Points 2 and 3

It does not appear that the examiner has challenged the effectiveness of MK-0677 itself. Rather, the Examiner implies that MK-0677 is too dissimilar to ghrelin to be considered

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<sup>2</sup> The specification specifically states that in the experiments described in Example 1, "the gastrectomy was accompanied by total vagotomy at the level of cardia".

probative that ghrelin would have the same effect: "applicant has argued that the pharmacological behavior of the following compound is much more indicative of what one should expect from ghrelin than ghrelin itself: MK-0677".

This is not true, the applicant have simply explained that MK-0677 is a well accepted analogue of Ghrelin (page 2, response submitted April 23, 2008) which is also stated in the previously filed evidence (Jansson declaration filed April 11, 2008, point 7).

As to what can fairly be inferred from the success with MK00677, we respectfully direct the examiner's attention to paragraph 9 of the Jansson declaration, stating that MK-0677 binds to the ghrelin receptor GSR-1a (the growth hormone secretagogue receptor). See Smith, "Growth Hormone Releasing Substances: Types and Receptors", Hormone Res., 51 (Suppl. 3):1-8 (1999); copy enclosed. Ghrelin is the endogenous ligand for GSR-1a, see Camina, "Regulation of ghrelin secretion and action", Endocrine, 22:5-12 (Oct. 2003), copy enclosed. This implies that ghelin would be expected to be active in circumstances in which MK-0677 is active.

The Examiner says on page 4 that we have declined to identify the passage in Arnold et al, al J. Neurosci 26:11052, 2006, made of record by the last amendment, which supports the conclusion that the behavior of MK-677 in ghrelin is "more indicative on what one should expect from ghrelin than ghrelin itself".

Arnold did not discuss MK-0677, and we never asserted that he had. Indeed, in the last amendment we commented, "(It is further noted that this Arnold article describes Ghrelin, and the discrepancies [with Asakawa] thus can not be attributed to the use of MK677 versus Ghrelin.)" Far from asserting that Arnold taught something about MK-0677, we said that Arnold's experimental findings were about ghrelin itself, and directly contradicted Asakawa's. We will discuss this further below.

Point 4

We have previously referred to Arnold et al 2006, wherein the results of the present application have been confirmed by a different group of scientists. See their figure 2, where a dose dependent increase in food intake is observed. The results are explained in details on page 11055 first column under the heading "Ghrelin-induced eating". Arnold et al. were well aware of the conflict of their results with the data previously published by Asakawa (see page 11058, 1st column, paragraph starting with "Our data contrasts...".) We will discuss their suggested explanation of the conflict in point 5.

Arnold was correctly cited for the proposition that Asakawa's finding that vagotomy inhibiting ghrelin stimulation of feeding was erroneous.

Furthermore, the efficacy of ghrelin is now confirmed by Dornovill de la Cour et al, 2005, Gastric Physiology, copy enclosed. The author J-O Jansson is inventor on the present application. The results demonstrate that **Ghrelin** enhances fat pad weight and prevented weight loss in gastrectomized mice (figure 4 and 5 and the result summary page 907).

Thus, two different research groups (De la Cour/Jansson and Arnold) agree that ghrelin can enhance body weight in gastrectomized (hence vagotomized<sup>3</sup>) mice, rebutting the prior negative report of Asakwawa.

Arnold cites Asakawa at page 11052, col. 2, line 15, and again at page 11058, cols. 1 and 2 (various locations). Note in particular the final paragraph, beginning "our data contrast with reports that vagal lesions reduce the eating-stimulatory effect of ghrelin in mice, rats and humans (Asawakawa et al., 2001....)" Arnold (2006) concludes that the "acute eating stimulatory effect of intraperitoneal ghrelin does not require vagal afferent signaling" (abstract).

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<sup>3</sup> See De la Cour, page 912, col. 1, acknowledging that the "Gx" mice "were also vagotomised").

Point 5

The reason for the discrepancy between our (and Arnold's) results and that of Asakawa is not known. A possibility is that the vagotomized animals in Asakawa's study were not in optimal physical condition at the time of the tests. For instance, these animals could have been unable to increase food intake due to considerations other than the vagotomy itself. This has been suggested in Arnold et al., page 11058, col. 2, first paragraph.

Another possibility is that the difference is attributable to the fact that we (and Arnold) performed both gastrectomy and vagotomy, whereas Asakawa only performed a vagotomy. This is suggested by de la Cour, page 912, col. 1, second full para. De la Cour adds, "conceivably, vagotomy impairs ghrelin stimulated meal initiation but not the long term effects of ghrelin on body fat."

In the last amendment, we speculated that the removal of the stomach during a gastrectomy may reduce the basal level of ghrelin more than does a vagotomy as performed by Asakawa.

We do not believe that it is extraordinary that different results are obtained by different groups working on the same or similar subjects. In science, it is not unusual to find that data obtained in the early phase of exploration of a new field of science is disputed by later received data. The old data may be discredited, or distinguished.

Regardless of the reasons why Asakawa didn't see ghrelin stimulation in vagetomized individuals and we did, applicants are entitled to rely on their own data, and the papers of Arnold and de la Cour, as evidence of enablement and utility.

The Examiner has also failed to respond to our argument, in the last amendment, that this rejection as stated is procedurally improper and therefore fails to apply the correct legal standard. This rejection questions whether ghrelin could ever, regardless of the dosage, etc., be useful or operable (see MPEP 2164.07((I)(A))) in a vagotomized individual, and thus we should

have received a dual 101/112 ¶1 rejection, with "utility" standards applied. Compare MPEP 2164.07(I)(A) second paragraph, regarding such dual rejections, with MPEP 2164.07, preamble, second paragraph, regarding other types of enablement rejections. We note that under the dual enablement/utility standards, the issue is whether it would have been **credible** to one skilled in the art that ghrelin be able to stimulate appetite in a gastrectomized and vagectomized individual. See MPEP 2164.07(I)(C), and the cited 2107.02(III)(B).

4.2. Finally, the Examiner argues that "prophylactically effective" is recited in claim 38, line 7, as well as in claim 41 and reads upon outright prevention.

The Examiner is correct that claim 38, line 7 as examined still asserted this, even though we deleted it from line 4, and we have now corrected claim 38.

But the larger issue is that the Examiner has completely ignored our argument (pp. 16-18 of the January 29, 2008 amendment) explaining why "prophylactically effective" does not be interpreted as **requiring** absolute prevention, and such argument applies equally to claim 41. We respectfully urge the examiner to now give proper consideration to that argument.

Respectfully submitted,

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